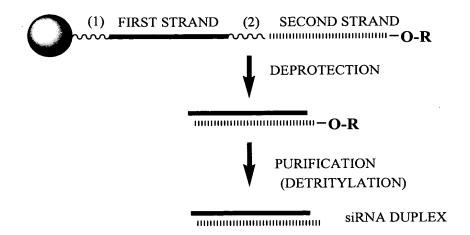
Title: RNA Interference Mediated Inhibition Of Hepatitis C Virus (HCV) Gene Expression Using Short Interfering Nucleic Acid (siNA) Attorney Docket No. MBHB02-763-B (400/129) Sheet 1 of 24

Figure 1



- = SOLID SUPPORT
 - R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)
- (1) = CLEAVABLE LINKER
 (FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
 (2) INVERTED DEOXYABASIC SUCCINATE)
- = CLEAVABLE LINKER

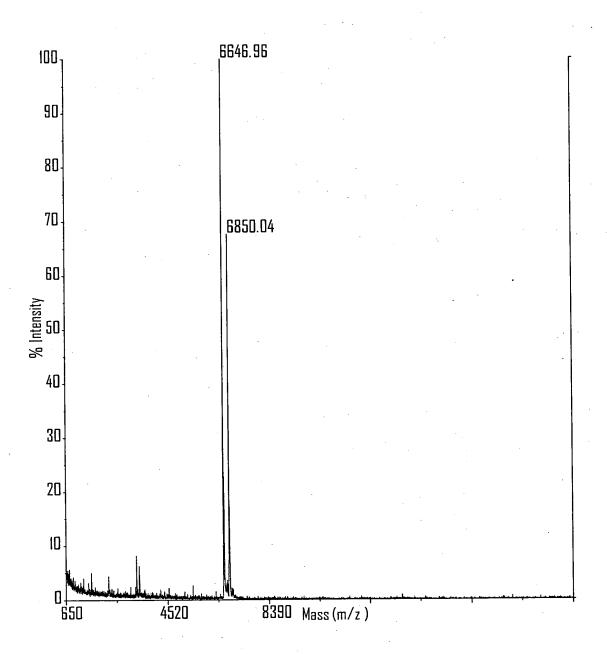
 (FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

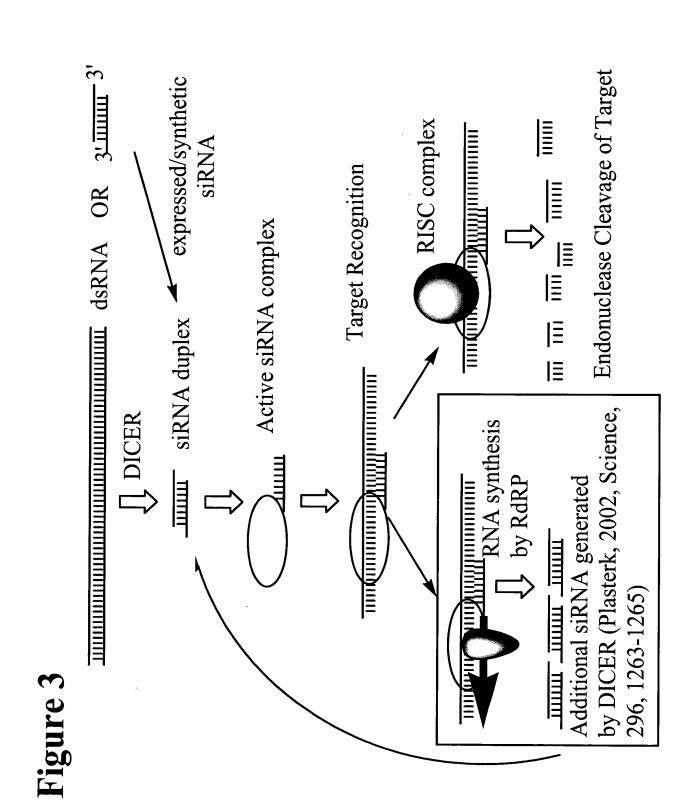
INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Title: RNA Interference Mediated Inhibition
Of Hepatitis C Virus (HCV) Gene Expression
Using Short Interfering Nucleic Acid (siNA)
Attorney Docket No. MBHB02-763-B (400/129)
Sheet 2 of 24

Figure 2





Title: RNA Interference Mediated Inhibition Of Hepatitis C Virus (HCV) Gene Expression Using Short Interfering Nucleic Acid (siNA) Attorney Docket No. MBHB02-763-B (400/129) Sheet 4 of 24

Figure 4

` '	3' 5'
5'- NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	3' 5'
3	3' 5'
5'- B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	3' 5'
3'- L-(N _s N) N N N N N N N N N N N N N N N N N N	, }
5'- B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	5'
	ALL POSITIONS RIBONUCLECTIDE EXCEPT POSITIONS (N N) 5'- B-N N N N N N N N N N N N N N N N N N

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

- B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
- L = GLYCERYL MOIETY THAT IS OPTIONALLY PRESENT
- S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

Title: RNA Interference Mediated Inhibition
Of Hepatitis C Virus (HCV) Gene Expression
Using Short Interfering Nucleic Acid (siNA)
Attorney Docket No. MBHB02-763-B (400/129)
Sheet 5 of 24

Figure 5

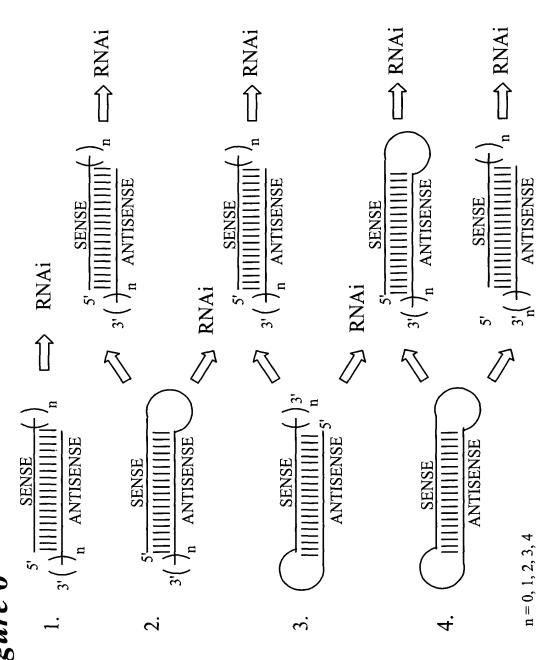
		SENSE STRAND (SEQ ID NO 1697))
A	5'- 3'-	iB- A C A C C G G A A U U G C C A G G A C T T-iB L-T _S T U G U G G C C U U A A C G G U C C U G ANTISENSE STRAND (SEQ ID NO 1698)	-3' -5'
В	5'-3'-	SENSE STRAND (SEQ ID NO 1699) acaccggaauugccaggacT _S T L-T _S Tuguggccuuaacgguccug ANTISENSE STRAND (SEQ ID NO 1700)	-3' -5'
C	5'- 3'-	SENSE STRAND (SEQ ID NO 1701) iB-A c A c c G G A A u u G c c A G G A c T T-iB L-T _S T u G u G G c c u u A A c G G u c c u G ANTISENSE STRAND (SEQ ID NO 1702)	-3' -5'
D	5'- 3'-	SENSE STRAND (SEQ ID NO 1703) iB-AcAccGGAAuuGccAGGAcTT-iB L-T _S Tuguggccuuaaccgguccug ANTISENSE STRAND (SEQ ID NO 1700)	-3' -5'
E	5'-	SENSE STRAND (SEQ ID NO 1704) iB-A c A c c G G A A u u G c c A G G A c T T-iB L-T _S T u g u g g c c u u <u>a</u> <u>a</u> c g g u c c u g ANTISENSE STRAND (SEQ ID NO 1700)	-3' -5'
F	5'-3'-	SENSE STRAND (SEQ ID NO 1703) iB-A c A c c G G A A u u G c c A G G A c T T-iB L-T _S T u G u G G c c u u A A c G G u c c u G ANTISENSE STRAND (SEQ ID NO 1705)	-3' -5'

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro italic lower case = 2'-deoxy-2'-fluoro underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
B = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE

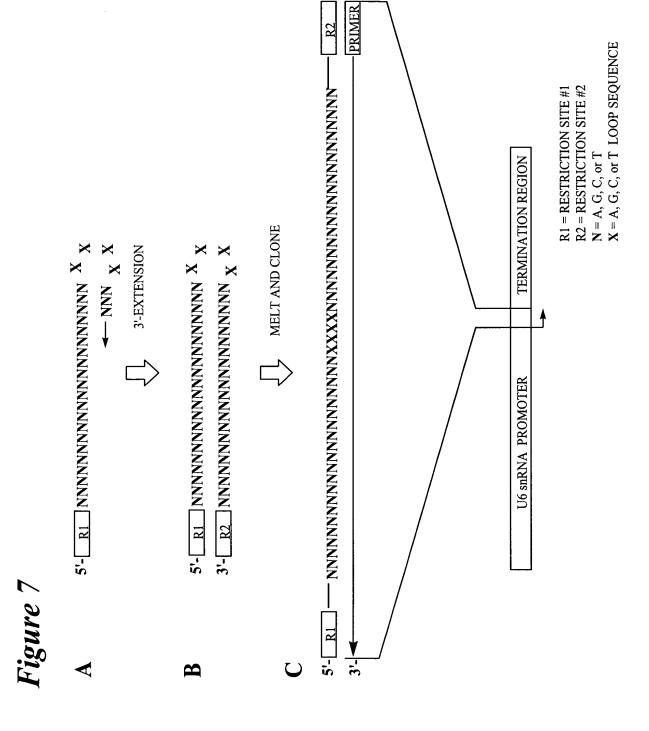
Inventor. James McSwiggen et al.
Title: RNA Interference Mediated Inhibition
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Using Short Interfering Nucleic Acid (siNA)
Attorney Docket No. MBHB02-763-B (400/129)
Sheet 6 of 24





Title: RNA Interference Mediated Inhibition
Of Hepatitis C Virus (HCV) Gene Expression
Using Short Interfering Nucleic Acid (siNA)
Attorney Docket No. MBHB02-763-B (400/129)
Sheet 7 of 24

<u>.</u>



Title: RNA Interference Mediated Inhibition Of Hepatitis C Virus (HCV) Gene Expression Using Short Interfering Nucleic Acid (siNA) Attorney Docket No. MBHB02-763-B (400/129) Sheet 8 of 24

Figure 8

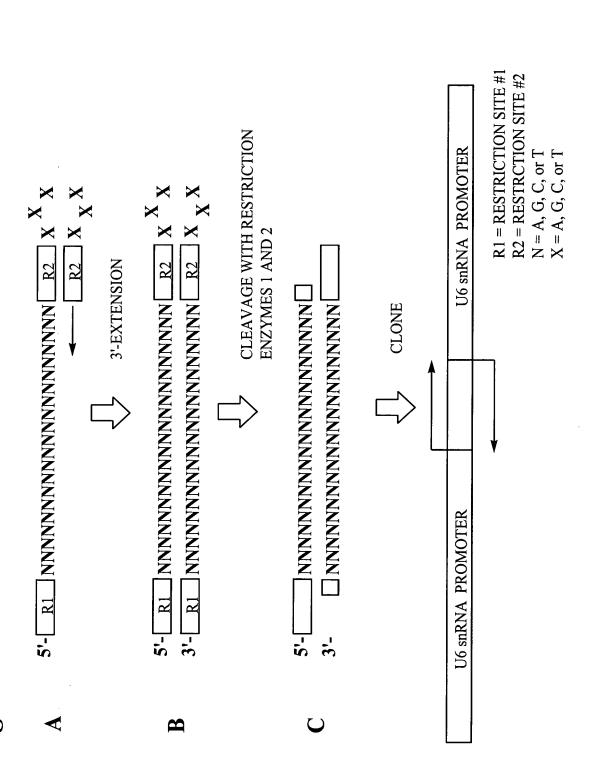
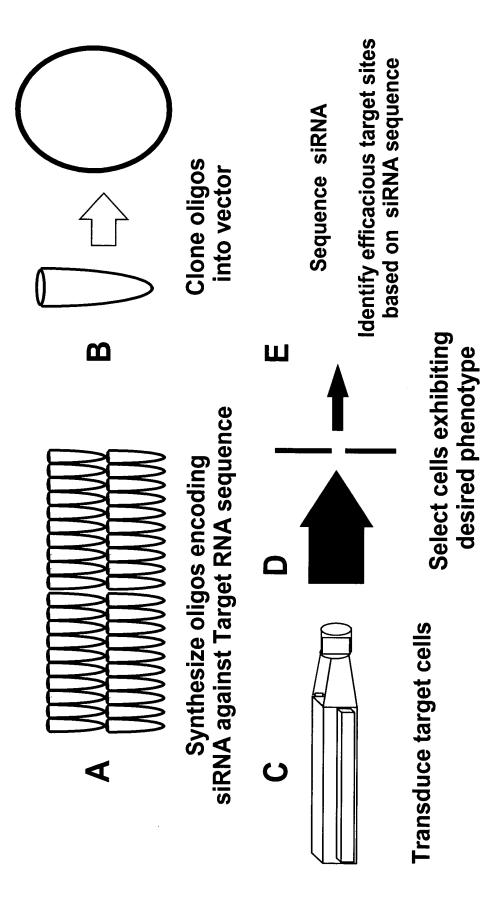
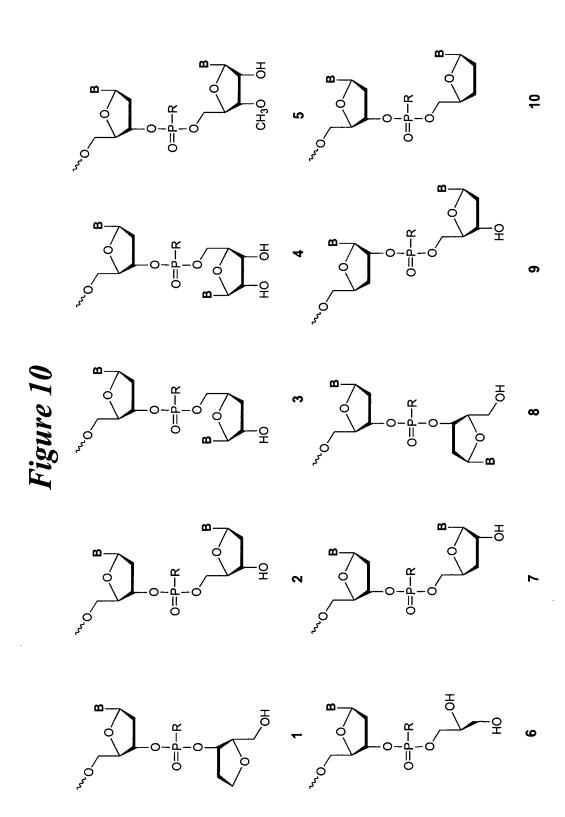


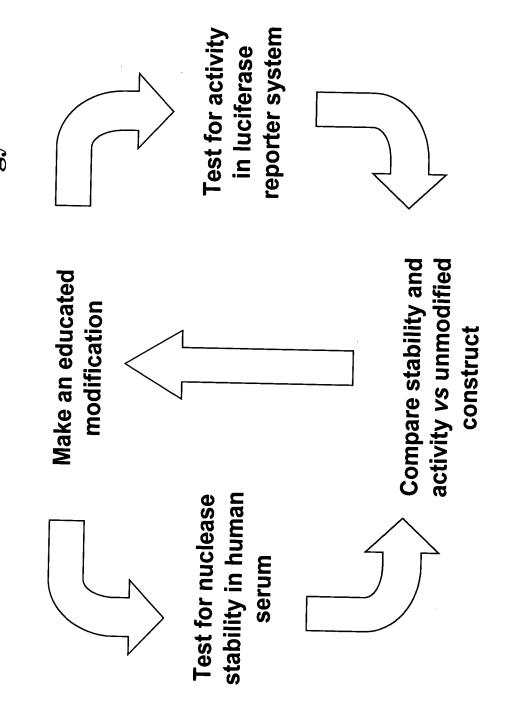
Figure 9: Target site Selection using siRNA

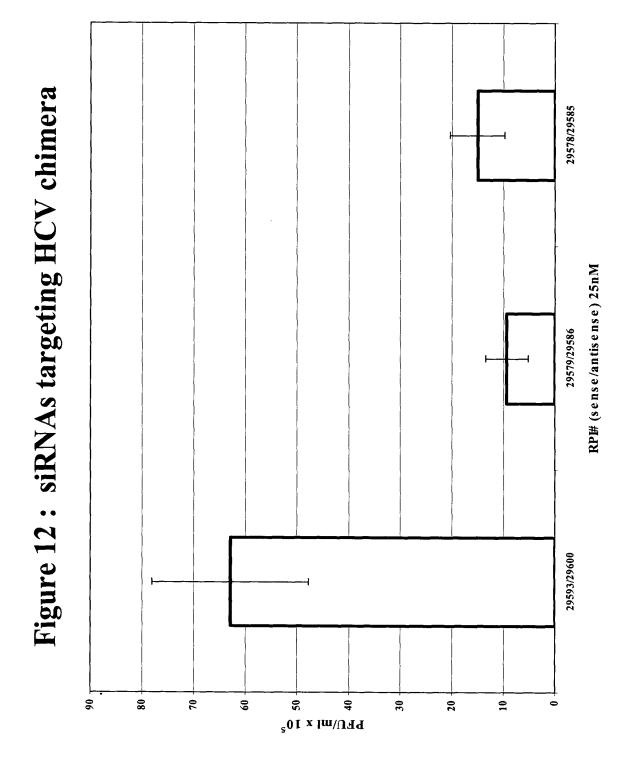


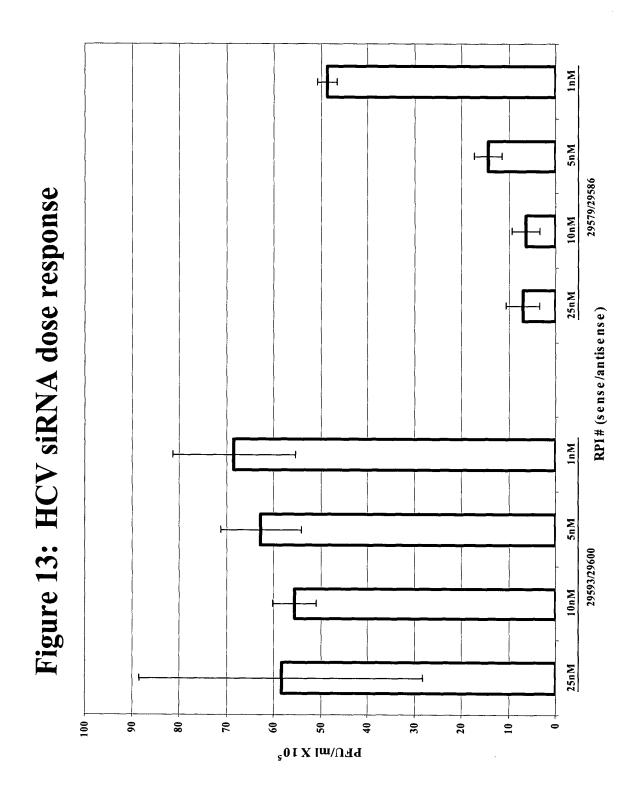


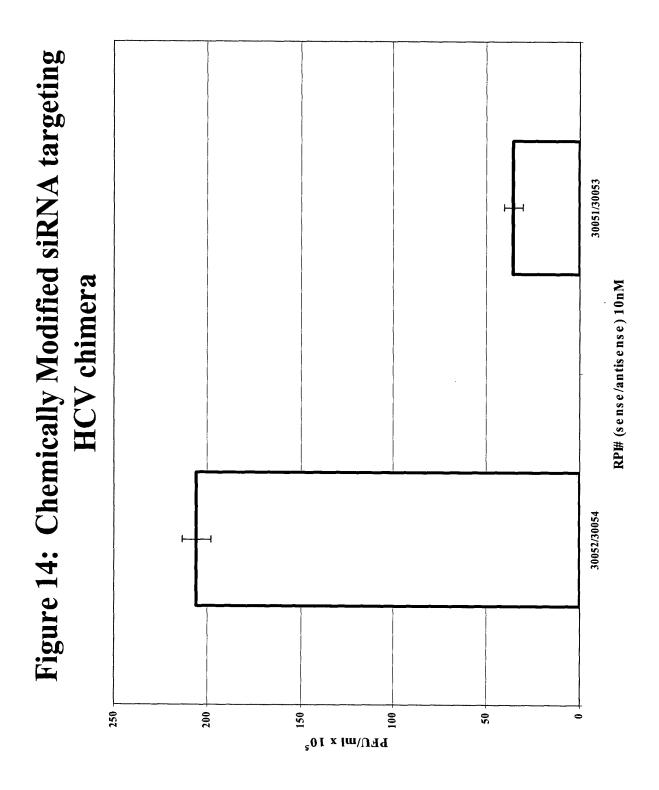
R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy









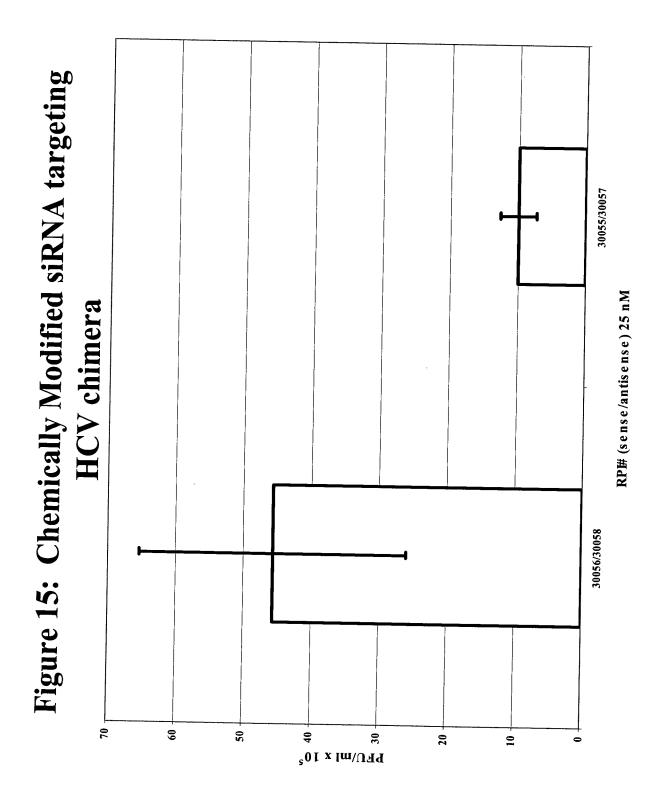


Figure 16: Chemically Modified siRNA targeting HCV chimera

HCV/PV#280-siRNA to HCV-Luc 325/345

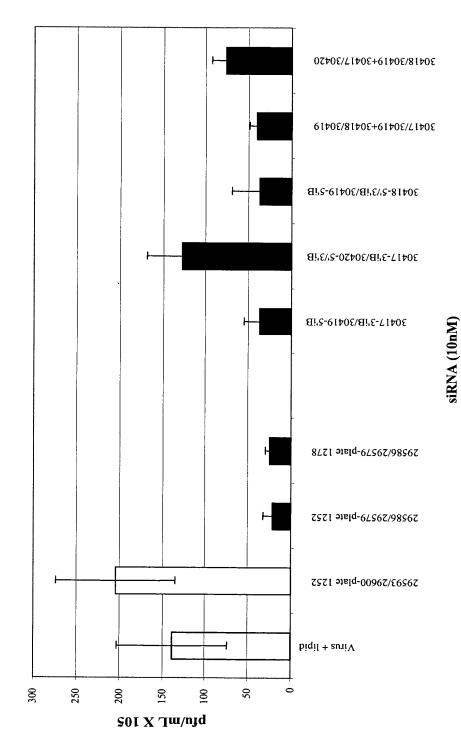
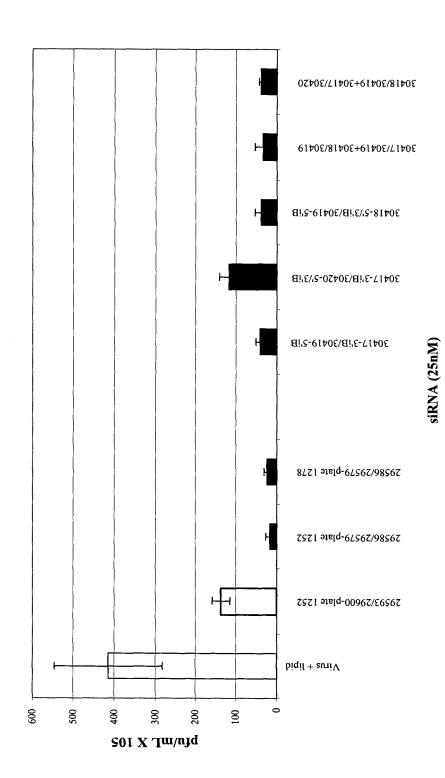
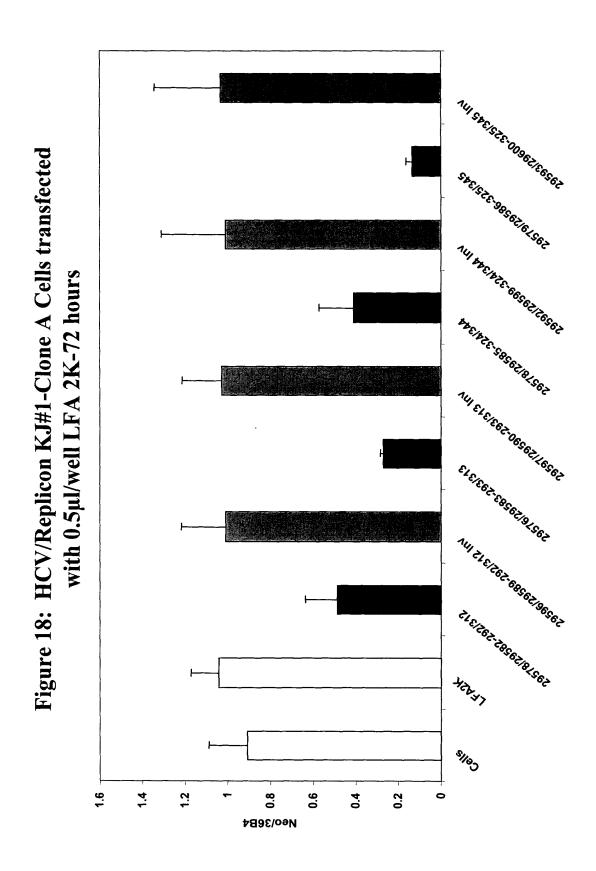
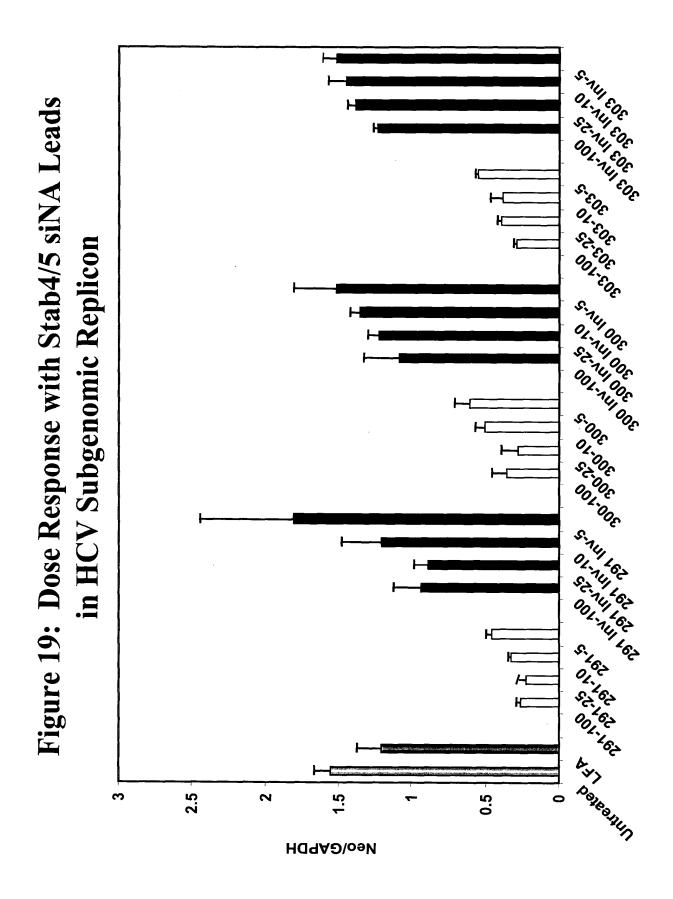


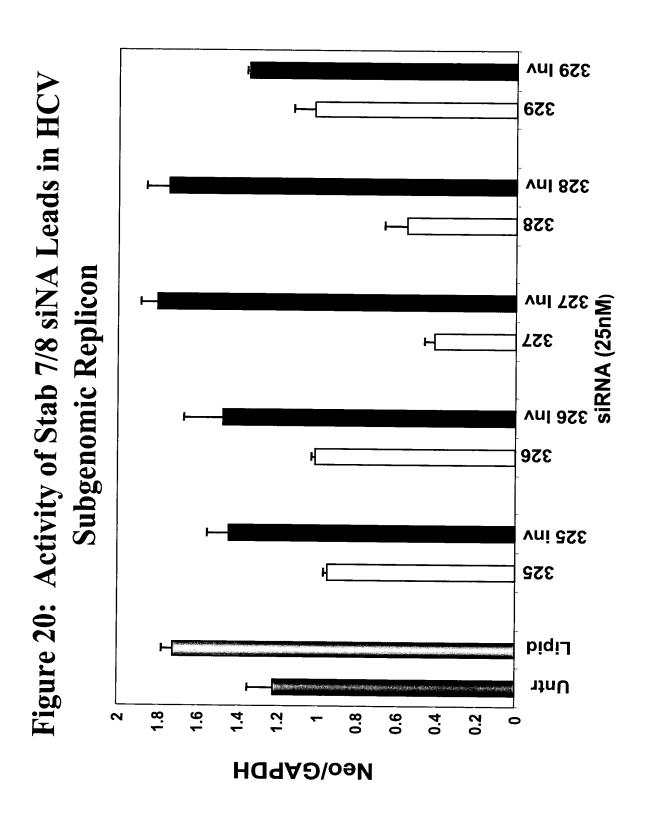
Figure 17: Chemically Modified siRNA targeting HCV chimera

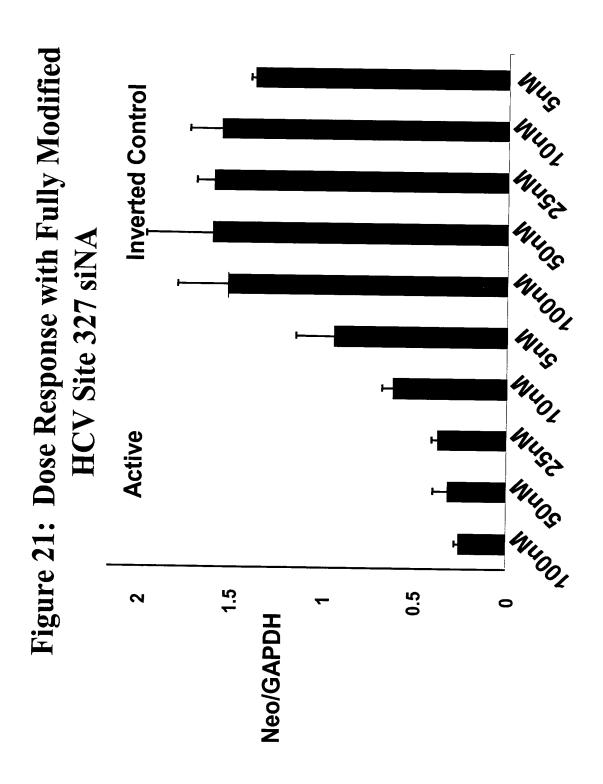
HCV/PV#280-siRNA to HCV-Luc site 325/345











Combination Treatment in HCV Replicon Figure 22: Activity of siNA/Interferon

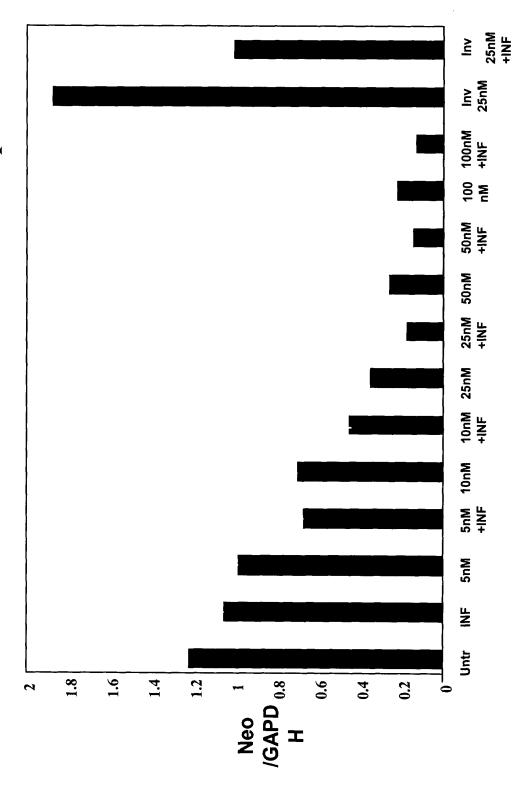
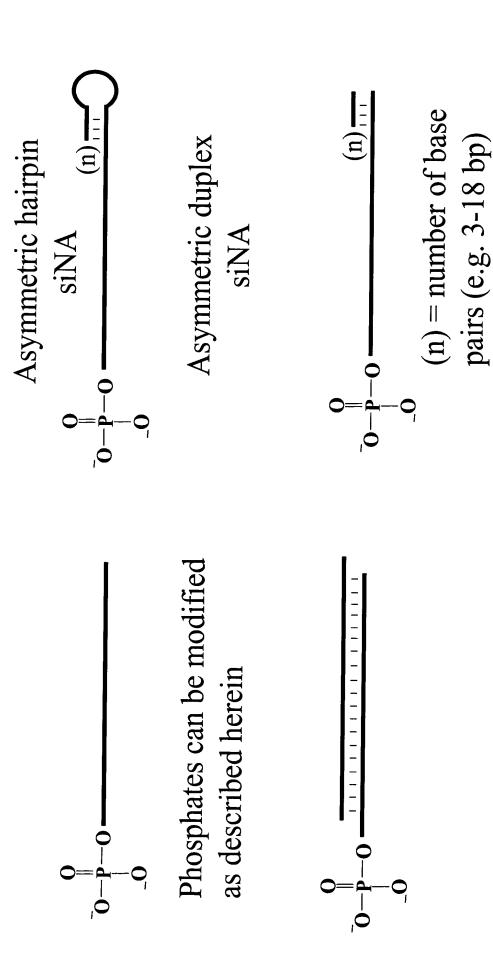


Figure 23: Phosphorylated siNA constructs



modifications herein

Figure 24: 5'-phosphate modifications

